REMARKS

Reconsideration is requested.

Entry of the attached Request for Continued Examination is requested along with entry of the Amendment of May 27, 2003 as well as the above.

The claims have been amended to include a further claim 59 which is believed to be supported by the specification. No new matter has been added.

As previously noted, the applicants believe and respectfully submit that the pending claims do not include a non-functional ribonucleotide reductase gene, as required by U.S. Patent No. 5,585,096, cited by the Examiner. Specifically, the claimed method of treatment requires injection of an avirulent herpes simplex virus type I (HSV-1), wherein the avirulent HSV-1 consists of an HSV-1 genome which is mutated in the γ34.5 gene.

In the attachment to the Advisory Action dated August 15, 2003, the Examiner asserts that "the consisting language is drawn only to the HSV-1 genome and not to a sole mutation in the γ34.5 gene." See, page 2 of the Advisory Action dated August 15, 2003 (Paper No. 38). Clarification is requested as the Examiner appears to be asserting that there are some other genes outside of the entire genome of HSV-1 which may include the ribonucleotide reductase gene of the cited patent. In the event the Examiner is requiring recitation of a single mutation in the γ34.5 gene, such should not be required to define over the cited art as the closed language of the claim excludes the non-functional ribonucleotide reductase gene required by the cited art. Nothing more should be required.

As for the Examiner's reference to R3616 in Paper No. 38, the applicants assume the Examiner is referring to the cited Markert (Neurosurgery, 1993, 32:597-603, as referenced on page 9 of the Office Action dated March 1, 2000 (Paper No. 21)) reference. As noted by the Examiner however Markert teaches, at best, that R3616 may be effective when tested in an intracranial glioma model, whereas the presently claimed invention is directed to a method of treating a metastatic tumour which occurs in but does not originate from the central nervous system of a human. The experiences and reports of Markert therefore are not believed to be relevant to the presently claimed invention.

More importantly, U.S. Patent No. 5,585,096, concerns only an HSV-1 mutated in both the γ34.5 and ribonucleotide reductase genes. The presently claimed invention is directed to a method of treating a metastatic tumour. The Examiner appears to repeatedly equate the capacity of a virus, such as HSV-1 to infect tumour cells with treatment of tumour cells. The Examiner is urged to appreciate however that a capacity to infect does not necessarily equate with or make obvious a capacity to treat such that the effect of infection is not necessarily known, especially from the cited art. It is well-known that a virus may be able to infect cells but nevertheless be unable to replicate in or lyse cells. For example, in the present application, it is shown that HSV 1716 can infect non-tumour bearing mouse brain, i.e., normal mouse brain cells, but not replicate in normal mouse brain cells (see, page 23, lines 16-19). Moreover, none of the cited art documents teach or suggest that mutant HSV can infect metastatic tumour cells.

U.S. Patent No. 5,585,096, contains no mention of metastatic tumours.

The Examiner is reminded that the presently claimed invention requires treatment of metastatic tumours.

Olofsson (Arch. Virol. 1993, 128:241-256), cited by the Examiner, teaches that HSV-1 infects metastatic melanoma. This references shows only that HSV-1 infects a melanoma cell line B-16, which is capable of metastasizing when transplanted into animals. Olofsson does not teach or suggest however that HSV-1 infects metastatic melanoma *in situ*.

None of the cited art cures these deficiencies of U.S. Patent No. 5,585,096, Olofsson or Markert.

Further, as explained above, one of ordinary skill in the art would not extrapolate from a finding that HSV will infect a tumour cell *in vitro* to a suggestion that HSV will be an effective treatment for that tumour. The applicants urge the Examiner to review the attached findings of Randazzo et al. (Virology 211, 94-101, 1995) in this regard wherein the authors describe that though B-16 cells could be infected by HSV, these cells were completely resistant to lysis by 4 HSV-1 isolates including wild-type and γ34.5 mutant HSV-1 (see, page 98, column 2, final paragraph of the attached).

Even assuming U.S. Patent No. 5,585,096 were an enabling reference, as repeatedly alleged by the Examiner, the specification of the patent teaches only that mutant HSV can be used in a treatment of glioma and non-nervous system primary tumours. U.S. Patent No. 5,585,096 does not teach or suggest that HSV can be used in a treatment of metastatic tumours of any kind, such as metastatic non-neuronal tumours occurring in the central nervous system, as required by the claims.

The claims are submitted to be patentable over the combination of U.S. Patent No. 5,585,096, Olofsson, Davey (Neurosurgery, 1991, 28:8-14), WO 92/13943 and Markert. Withdrawal of the Section 103 rejection and allowance of the pending claims are requested.

The Examiner is also further requested to reconsider the new matter rejection which is apparently again repeated in Paper No. 38. The Examiner now appears to object to the Amendment because the "incorporation by reference statement must be included in the specification-as-filed...". See, page 3 of Paper No. 38. The Examiner is urged to appreciate that page 4, lines 3-10 of the originally-filed specification (filed as PCT/GB95/01791, which designated the U.S.) state as follows:

> "The construction of mutant virus 1716 as described in published patent application WO 92/13943 (PCT/GB92/00179) the contents of which are incorporated herein by reference. However this patent publication is solely concerned with the use of mutant 1716 as a vaccine, either in itself or as a vector vaccine which includes a heterologous gene coding for an antigen."

The applicants have been making every attempt to amend the specification to include the subject matter incorporated by reference in the original application since January 22, 2001. The undersigned respectfully submits that all of the requirements for incorporation by reference and amendment of the specification to include the same have been complied with. The originally-filed specification, filed as a PCT application which designated the U.S., did, in fact, include an incorporation by reference at page 4, as cited above, to PCT/GB92/00179. The Examiner is urged to reconsider again this rejection and withdrawal the same. The undersigned would be happy to discuss the

matter by telephone or in person if the Examiner would find it useful in considering the requirements relating to incorporation by reference and this outstanding rejection.

The application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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